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Assessment of fetal maturation age by heart rate variability measures using random forest methodology

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ABSTRACT

Fetal maturation age assessment based on heart rate variability (HRV) is a predestinated tool in prenatal diagnosis. To date, almost linear maturation characteristic curves are used in univariate and multivariate models. Models using complex multivariate maturation characteristic curves are pending.

To address this problem, we use Random Forest (RF) to assess fetal maturation age and compare RF with linear, multivariate age regression. We include previously developed HRV indices such as traditional time and frequency domain indices and complexity indices of multiple scales.

We found that fetal maturation was best assessed by complexity indices of short scales and skewness in state-dependent datasets (quiet sleep, active sleep) as well as in state-independent recordings. Additionally, increasing fluctuation amplitude contributed to the model in the active sleep state. None of the traditional linear HRV parameters contributed to the RF models. Compared to linear, multivariate regression, the mean prediction of gestational age (GA) is more accurate with RF than in linear, multivariate regression (quiet state: $R^2 = 0,617$ vs. $R^2 = 0,461$, active state: $R^2 = 0,521$ vs. $R^2 = 0,436$, state independent: $R^2 = 0,583$ vs. $R^2 = 0,548$).

We conclude that classification and regression tree models such as RF methodology are appropriate for the evaluation of fetal maturation age. The decisive role of adjustments between different time scales of complexity may essentially extend previous analysis concepts mainly based on rhythms and univariate complexity indices. Those system characteristics may have implication for better understanding and accessibility of the maturating complex autonomic control and its disturbance.

1. Introduction

Since heart rate patterns are one of the few signals obtainable from the fetus easily and non-invasively, they are predestinated for assessing the maturating fetal autonomic control and its disturbances [1–5]. The complex behavior of the maturating fetal autonomic nervous system (ANS) was recently described by means of corresponding heart rate variability (HRV) indices. However, the maturation itself is a complex and non-linear process. Interpretation of non-linear complexity characteristics is ambiguous and has been discussed with the formation of fetal behavioral states [6–8]. On the basis of changes in the power spectra, van Leeuwen et al. showed that maturation is characterized by non-linear characteristics [9] and different stages of fetal development were discussed in association with the increasing influence of the different branches of the ANS [3,10]. However, to date the complex maturation process was mainly approximated by linear characteristic curves in univariate regression models using linear and non-linear HRV indices [6,9–11]. The investigation of the performance of the best predicting HRV indices in a multivariate model using non-linear and complex maturation characteristic curves is pending. Hoyer et al. recently proposed a fetal autonomic brain age score (fABAS) for the assessment of fetal age, based on MLR models according to universal developmental characteristics [12,13]. However, parameter selection for MLR models in these investigations was based on a pre-selection of HRV indices. Since even the maturation characteristic curves are not known and they can be different for different HRV indices, a complex non-linear approach without pre-setting is required.

With regard to that, classification and regression tree (CART) methodology such as Random Forest (RF) may provide potential advantages [14]. The non-linear and complex data structures of RF provide an ambitious technique for data mining, e.g. in geoinformatics [15,16] or computational biology [17–19]. A direct

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comparison between ordinary linear regression and RF was done by Nir et al., who investigated the performance of both models for the assessment of the nociception level under anesthesia [20]. They found that the advanced, non-linear approach performed better than linear regression. However, a general statement on the superiority of RF compared to other linear and non-linear models is limited due to the fact that the accuracy of predictions is biased by different methodological approaches and results heavily depend on the underlying problem [21]. With respect to clinical applications, researchers often try to obtain as much information as possible from the investigated process. Modeling such processes with common linear methods requires previous knowledge of interactions between variables and explicit modeling of non-linearities. RF as a non-linear, multivariate regression and classification methodology is able to overcome this problem, even when values are missing [14]. Additionally, the assessment of the parameter importance employed in RF provides a beneficial tool for the identification of important variables avoiding pre-selection of HRV parameters on the basis of single characteristic curves. Single applications of RF to heart rate time series in adults have been reported with satisfying results, e.g. in connection with sleep state classification [22], classification of cardiac rhythms [23], risk stratification for arrhythmic cardiac death [24], or the prediction of cardiovascular and cerebrovascular events [25]. As far as is known to the authors, the only application of RF in the context of fetal development was published by Peterek et al. who classified pathological, suspect and normal fetal states based on cardiotocography (CTG) measurements [26]. However, due to its restricted temporal resolution, CTG is of limited appropriateness for the precise assessment of fast heart rate modulation [27]. According to the “developmental origins of adult disease (Barker) hypothesis” (also known as fetal programming) [28], the precise evaluation of the normal development is important with respect to the early identification of fetal developmental disorders since these have implications for health problems in later life which cannot completely be compensated for by later postnatal therapies [29].

The objective of the present work is to evaluate the capability of a complex maturation model, using previously developed HRV indices obtained from high resolution fetal magnetocardiographic (fMCG) recordings and complex maturation functions to predict fetal gestational age (GA) for the assessment of normal fetal development. Further, we compare results of GA prediction from RF methodology with linear, multivariate age regression.

2. Methods

2.1. Subjects

359 fMCG recordings were taken from healthy, singleton fetuses with an age between 21–41 weeks of gestational age (WGA). Recordings from subjects with intrauterine growth restriction, non-reassuring non-stress test based on conventional CTG, known chromosomal abnormalities or congenital abnormalities based on ultrasound diagnosis, fetal arrhythmia or previous exposure to synthetic steroids in utero were not considered for analysis. Additionally, maternal exclusion criteria were: administration of cardiovascular effective drugs, cardiovascular diseases, diabetes. The study was approved by the local ethics committee of the Friedrich Schiller University. All women signed a written, informed consent form.

2.2. Data acquisition and pre-classification of fetal behavioral states

The fMCG measurements were taken at the Biomagnetic Center in a magnetically shielded room using the vector-magnetograph ARGOS 200 (ATB Chieti, Italy). In order to prevent compression of the inferior vena cava, the pregnant women were positioned supine with a slight twist to either side. The fetal heart was localized by sonographic measurements prior to the fMCG recording. Afterwards, the dewar was positioned contactless as close as possible to the fetal heart. In the next step, the fMCG-signal was recorded for 30 min at a sampling rate of 1024 Hz. For fetal heart beat detection we used an own toolbox [41,42]. Incorrectly detected beats (less than 2%) were linearly interpolated resulting in artifact free normal-to-normal (NN) interval series. After signal preprocessing (signal preprocessing toolbox, BMDSys, Jena) the NN interval series were independently pre-classified by three collaborators into 10-minute state specific heart rate pattern (HRP), referring to quiet sleep (HRP I, $n=111$) and active sleep (HRP II, $n=248$) according to [43]. Pre-classification of these two HRP was based on the criteria proposed by Schneider et al. [44] applicable throughout the second half of gestation.According to the Maternity Guidelines of Germany (FIGO, 2011), the gestational age was determined based on the history of the last menstrual period and confirmed by obligatory first trimester ultrasound screening between 9 and 12 weeks of pregnancy. The ultrasound results were taken from the maternity documents.

2.3. HRV parameter set

The selection of HRV parameters for multivariate age regression was based on previous investigations of HRV parameters and their relation to the fetal development in our own group [3,6,7, 10,12,13,44,33,38,39]. The selected parameter set consisted of parameters from traditional signal analysis methods in the time- and frequency domains according to the guidelines of the HRV Task Force [30], but also included parameters obtained from methods with a non-linear approach such as multiscale (MSE) complexity [36], asymmetry [40] and fractal scaling [32] (see Table 1). Table 1 shows the selected HRV parameters. A more detailed explanation and their interpretation can be found in [12,13].

2.4. Regression models

Fetal maturation age was predicted by multivariate linear regression (MLR) and RF models for each state (HRP I, HRP II) and for state independent measurements (30 min). The models were 70/30 split sample cross-validated. Model prediction accuracy was determined by the mean of the corrected coefficient of determination (R^2) from regression of predicted maturation age and real maturation age in WGA. Forward procedure (stepwise inclusion of variables while $P<0.05$) and backward procedure (stepwise exclusion of variables while $P>0.1$) was used in MLR models.

In RF models, each decision tree of the forest was built by using a random bootstrap sample of 2/3 of the training set and a randomly selected number of predictors m_{try} for splitting at each node in the tree. The remaining 1/3 samples of the training set (out-of-bag samples, OOB) were used to calculate an unbiased prediction error *OOBerror* which allowed to validate the model accuracy during training and to calculate absolute values of parameter importance. Relative parameter importance is calculated as the increase in prediction error if the values of the parameter are permuted across the *OOB*-observations. The more the prediction error increases, the more important is the particular parameter. This relative importance is computed for every tree and averaged and divided by the standard deviation over the entire ensemble. Relative parameter importance was used to define the final parameter set in the RF model: The parameters with the smallest parameter importance were stepwise discarded and afterwards the *OOBerror* calculated. The final parameter set was the one